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Hypoglycemic effect of disopyramide in a case of diabetes mellitus under insulin treatment.

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Abstract

In a 41-year-old male with diabetes mellitus well controlled with insulin (50 units/day), hypoglycemia developed after starting disopyramide treatment (200 mg/day) for correction of tachycardia. Lower levels of blood glucose and smaller amounts of urinary sugar persisted until disopyramide was withdrawn even after reducing insulin to a minimum dose of 20 units/day. The insulin requirement increased again thereafter to the original dose. These results indicate that disopyramide had a hypoglycemic effect in this patient.

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—— BRIEF NOTE ——

HYPOGLYCEMIC EFFECT OF DISOPYRAMIDE IN A CASE OF DIABETES MELLITUS UNDER INSULIN TREATMENT

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Abstract. In a 41-year-old male with diabetes mellitus well controlled with insulin (50 units/day), hypoglycemia developed after starting disopyramide treatment (200 mg/day) for correction of tachycardia. Lower levels of blood glucose and smaller amounts of urinary sugar persisted until disopyramide was withdrawn even after reducing insulin to a minimum dose of 20 units/day. The insulin requirement increased again thereafter to the original dose. These results indicate that disopyramide had a hypoglycemic effect in this patient.

Key words: disopyramide, hypoglycemia, diabetes mellitus, insulin.

Disopyramide (α-(2-diisopropylaminoethyl)-α-phenyl-2-pyridineacetamide, Rythmodan®, Chugai Pharmaceutical Co.), an anti-arrhythmic agent similar to but more potent and dependable than quinidine (1), was considered to have caused hypoglycemia in a patient on insulin treatment for diabetes mellitus. The possible adverse reaction was reported to Chugai Pharmaceutical Co. in May 1978 and had been investigated by the company with the following results: a) Searle Co. became aware of the hypoglycemia problem after marketing in the United States and reported in Scrip No. 369, March 17, 1979, p. 13 that there was a tendency to lower blood sugar in the fasting state and possibly some enhancement of reactive hypoglycemia in human volunteers. b) Experiments performed with rats by Chugai Pharmaceutical Co., as indicated by the Japanese Ministry of Walfare based on the above report, revealed a dose-related hypoglycemia and an increase in plasma insulin level (2). c) Hypoglycemic coma which developed in a case of malignant lymphoma in relation to the use of disopyramide phosphate was presented by Watanabe *et al.* (3) at the 298th Kanto-district meeting of the Japanese Society of Internal Medicine held in December 1979.

Based on these facts, the Japanese Ministry of Welfare recommended that hypoglycemia be listed as a possible adverse reaction of disopyramide (2).

Since no detailed case report is available even under these circumstances, the authors feel that it is worth-while to present a case which illustrates the hypoglycemic effect of disopyramide.

Case report. A 41-year-old male clerk visited Yamamoto-Naika-Hospital because of weakness, emaciation and thirsty. He was admitted to the hospital on October 13, 1977 with positive urinary glucose and ketone bodies. His body weight on admission was 32 kg with otherwise unremarkable physical findings; height 154 cm, blood pressure 118/80 mmHg, pulse rate 84/min, mental status clear and tendon reflexes well retained. Laboratory examination revealed blood glucose levels in 50 g oral glucose tolerance test of 243 mg/100 ml at 0-time, 295 at 30 min, 375 at 1 h, 278 at 2 h and 279 at 3 h with strongly positive urinary glucose and less than 1 μ unit/ml IRI at all times, serum cholesterol 129 mg/100 ml, triglycerides 56 mg/100 ml, urea nitrogen 10 mg/100 ml, uric acid 2.0 mg/100 ml, Na 146 mEq/1, K 3.7 mEq/1 and erythrocyte sedimentation rates 2 and 8 mm in 1 and 2 h, respectively. The results of liver function tests, including protein fractions and serum enzymes, were within normal limits. No anemia, leukocytosis, proteinuria or impaired vision was present. Chest X-ray films disclosed emphysematous lungs and an electrocardiogram demonstrated a sinus tachycardia. The patient did not smoke tobacco or drink alcohol.

Daily excretion of urine sugar was calculated to be 23 to 58 g with an allowed carbohydrate intake of 277 g in a total caloric intake of 2000 Cal under a moderate physical exercise. Insulin treatment was instituted as indicated in Fig. 1 and the carbohydrate intake was reduced to 229 g with a total caloric intake of 1800 Cal. With 60 units of Rapitard insulin, fasting blood glucose levels decresed to around 100 mg/100 ml with less than 12 g of daily excreted urine sugar (February 7–22, 1978). Reduction of insulin to a daily dose of 50 units was reflected by a transient but definite rises in blood glucose and urine sugar, the latter ranging from 19–49 g a day (February 23-March 10, 1978). After replacing Rapitard insulin by the same units of Lente insulin, urinary excretion of sugar became much less and the fasting blood glucose level fell to 70 mg/100 ml (April 22, 1978). Increased pulse rates over 100/min remained even after normal glucose metabolism was restored and body weight had increased from 32 to 39 kg. Thyroid gland function was not hyperactive as revealed by normal T_3 and T_4 levels.

In an attempt to suppress the increased heart rate, 200 mg/day of disopyramide was started in two equally divided doses on April 22, 1978. Since a low fasting blood glucose level of 64 mg/100 ml was found thereafter, the dose of insulin was reduced to 40 units. Nausea with a slightly elevated blood pressure of 130/80 mmHg was noted two days later and a postprandial blood glucose level of 74 mg/100 ml was obtained. The nausea improved after oral administ-

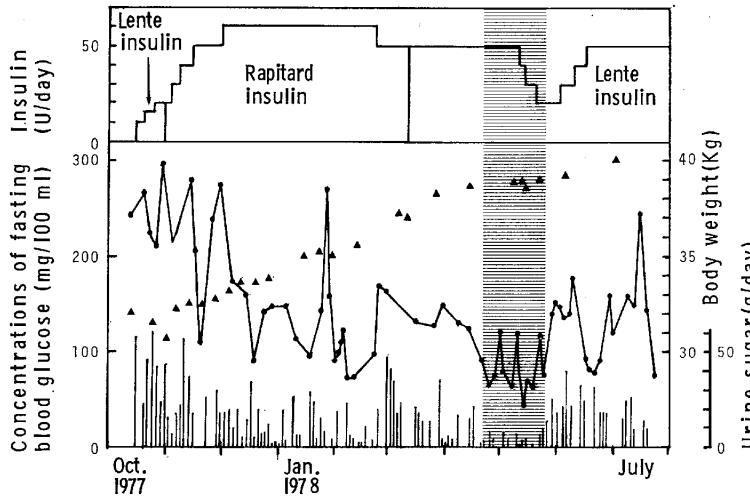

Fig. 1. Effect of disopyramide and insulin administration on fasting blood glucose and urine sugar levels. ●——●, concentration of fasting blood glucose; vertical bar, amount of urine sugar excreted (two negative results not included); ▲, body weight; and shaded area, the period of disopyramide administration (200 mg/day). Concentrations of blood glucose were determined by a glucose-oxidase method with a reagent kit prepared by Wako-Junyaku-Kogyo Co., Osaka and those of urine sugar by the method of Somogyi (4).

ration of 5 g of sugar. Since the fasting blood glucose level decreased further to 44 mg/100 ml next morning, insulin was reduced to 30 units and then to 20 units with still low values of fasting blood glucose and less than 10g/day of urine sugar. Disopyramide was withdrawn on May 25, 1978, because it not only failed to lower the pulse rate appreciably but also appeared to be related to the hypoglycemic episode. The concentration of blood glucose and the urinary excretion of sugar increased immediately after withdrawal of disopyramide. Urine sugar excretion ranged from 14 to 40 g/day (May 27-June 6, 1978). Fifty units of insulin was again required to maintain the fasting blood glucose level between 74 and 240 mg/100 ml with less than 9 g of daily excreted urine sugar (July 14–22, 1978). The patient was discharged on July 24 for ambulatory insulin treatment.

Comment. One possible explanation of the hypoglycemia observed during the addition of disopyramide to this patient's insulin treatment is a delayed or time-dependent effect of insulin on the blood glucose level as is usually observed in diabetic paitents after initiating insulin administration. However, this is unlikely because of the following observations: a) The reduction of insulin by 10 units before disopyramide administration resulted in marked increases in urinary sugar excretion and blood glucose level, while the reduction of insulin by 30 units during disopyramide treatment had no such effect until disopyramide

administration was discontinued. b) The dose of insulin required to control glucose metabolism increased again to the original dose of 50 units/day after withdrawal of disopyramide. These facts clearly indicate that disopyramide had a hypoglycemic effect at least in the presence of a small amount of insulin, which by itself was not sufficient to reduce the blood glucose level to the normal range.

The hypoglycemic effect of disopyramide appears to be related to the insulin secretion in experimental animals (2). Whether this applies to the hypoglycemia observed in the present case can not be assessed from the available data. An increased IRI level of 80 μ units/ml with a low glucose level of 30 mg/100 ml has been reported in a patient with malignant lymphoma who was on disopyramide (3). The β-blocker lowers blood glucose level by potentiating the action of insulin. However, disopyramide has no activity of blocking the β-adrenergic receptor (5).

In spite of the fact that disopyramide has been used widely in treating paroxysmal tachycardia and arrhythmias of atrial and ventricular origins, no report dealing with the hypoglycemic effect is available other than those stated in this communication. The present case had no unusual features of diabetes mellitus; the patient was a relatively late-onset type of insulin-dependent, non-obese diabetic without significant complications. The hypoglycemia due to disopyramide was probably too mild to be apparent to the patient without awareness of such effect.

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